**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In Re Application of: Chow et al.<br>Customer No.: 51957<br>Serial No.: 10/039,827<br><br>Filed: October 19, 2001<br><br>For: METHODS AND COMPOSITIONS FOR MODULATING ALPHA ADRENERGIC RECEPTOR ACTIVITY | Group Art Unit: 1614<br><br>Confirmation No. 9534<br><br>Examiner: Fay, Z. |

## BRIEF ON APPEAL

Dear Sir:

This appeal is taken from the rejection of all of the claims in an Examiner's action mailed April 19, 2007. Oral hearing is waived.

## (1) REAL PARTY IN INTEREST

The real party in interest is Allergan, Inc, having its principal place of business at 2525 Dupont Drive, Irvine, CA 92612.

## (2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences for this case.

## (3) STATUS OF CLAIMS

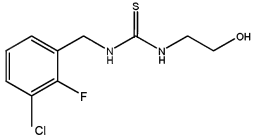
| Claims | Status |
|---|---|
| 1-3 | Rejected |
| 4-6 | Withdrawn |

## (4) STATUS OF AMENDMENTS

No amendments have been made after the final rejection.

## (5) SUMMARY OF THE CLAIMED SUBJECT MATTER

The claims are drawn to a compound, and compositions containing the compound, of the structure:




and esters and salts thereof. (Specification p. 7, formula 2).

## (6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

### Obviousness

Examiner erred in rejecting claims 1-3 as obvious under 35 U.S.C. § 103.

## (7) ARGUMENT

Examiner erroneously rejected claims 1-3 as being obvious in view of GB Patent 1499485 to Reiter ("Reiter") by failing to make a *prima facie* case of obviousness and by ignoring evidence of unexpected results presented in the patent application. "The

examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." MPEP 2142. In assessing obviousness, the Examiner must consider both the prior art and any evidence of secondary considerations such as unexpected properties of the claimed invention. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). Examiner has not provided any substantive explanation as to why the cited art renders the claimed composition obvious. Nor has Examiner considered that the patent application shows that the claimed compound reverses allodynia while the closest prior art compound does not. For these reasons, the inventions defined by the claims are not obvious, and the Board should direct Examiner to allow the claims.

**A. REITER DOES NOT RENDER THE CLAIMED COMPOUND *PRIMA FACIE* OBVIOUS.**

Examiner has not adequately explained how GB 14499485 renders the claims obvious. Examiners are required to make a *prima facie* case of obviousness using the *Graham* test. MPEP 2141. The *Graham* test requires Examiners to determine the scope and contents of the prior art, ascertain the difference between the prior art and the claims at issue, resolve the level of ordinary skill, and consider objective evidence present in the application indicating obviousness or non-obvious. MPEP 2141. "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). *KSR v. Teleflex*, 550 U.S. ___ (2007) citing *In re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006).

Examiner has merely made the conclusory statement that since the cited reference discloses "the genus encompassing the claimed compound," it is obvious. However, this genus contains approximately $3.8 \times 10^{34}$ compounds. To say that the genus disclosed in Reiter renders the presently claimed compound *prima facie* obvious

is like saying that it would be obvious to pay a visit to a single person listed in a phone book containing all the people living on $10^{24}$ planet Earths! Examiner must do more.

Examiner should have done, but did not do, a *Graham* analysis. This is what the Examiner says that relates to the scope of the prior art and the claims at issue: "[t]he GB Patent teaches the claimed compound as a species of a genus having a diuretic and saluretic effect." This is merely a conclusory statement and contains no factual particulars about the actual scope of the prior art required in a Graham analysis. Examiner has not described the scope of the prior art or shown how the claimed composition is similar to what is taught or suggested in the prior art. There is not even enough factual support to establish that the claimed compound does in fact fall within the genus as alleged.

Even if Examiner had established that the claimed compound feel within the genus described by the prior art, Examiner has not pointed to anything in the prior art that narrows the focus in the direction of the claims. The "genus having a diuretic and saluretic effect" is the genus including all of the compounds within the scope of the disclosure. For example, the reference says "[t]he diuretic and saluteric effects of certain of the compounds of general formula (I) are shown in Table II." (p. 2, right column, lines 83-94.) Formula I covers the entire disclosure. Thus, this statement does not narrow the genus in any way. Examiner has not explained at all how the "diuretic" and "saluretic" effects of the compounds in the cited reference have any bearing on what the reference teaches or suggests. Thus, this appears to be a red herring, a mere distraction from any relevant argument.

The remaining required elements of the Graham analysis are similarly absent from the rejection. There is no assessment of the level of ordinary skill in the art. Finally, Examiner did consider the objective evidence present in the patent application

indicating obviousness or non-obviousness. Thus, Examiner has not made a *prima facie* case of obviousness.

The following is the method used to estimate the number of compound encompassed by Reiter. The assumptions made actually make the estimate low by several orders of magnitude.

$R^1$, $R^2$, and $R^3$ each have the following possible groups (see p. 1, left column, lines 55-69):

1. hydrogen (1 possibility)
2. $C_{1-8}$ hydrocarbyl (471 possibilities)
3. $C_{1-8}$ substituted with one or more halogens (1884 possibilities)
4. hydrocarbylaminohydrocarbyl (221,841 possibilities)
5. dihydrocarbylaminohydrocarbyl (52,243,555 possibilities)
6. hydrocarbyloxy (471 possibilities)
7. hydrocarbyloxy which has one or more halogen substituents (1884 possibilities)
8. hydroxyl group (1 possibility)
9. dihydrocarbylamino (110,920)
10. acylamino (1 possibility)
11. nitro group (1 possibility)
12. sulfonic acid group (1 possibility)
13. halogen atom (4 possibilities)

These add up to 52,581,035 possibilities for each of $R^1$, $R^2$, and $R^3$.

$R^4$ has the following possibilities (see p. 1, left column, lines 70-74):

1. hydrogen (1 possibility)
2. $C_{1-8}$ hydrocarbyl (471 possibilities)
3. $C_{1-8}$ hydrocarbyl with one or more hydroxyl substituents (471 possibilities)

These add up to 942 possibilities.

$R^5$ has the following possibilities (see p. 1, left column, lines 75-80):

1. $C_{2-6}$ straight or branched chain aliphatic hydroxyhydrocarbyl (32 possibilities)

2. $C_{3-6}$ hydrocarbyl (30 possibilities)

These add up to 62 possibilities.

$R^6$ has the following possibilities (see p. 2, right column, lines 1-10):

hydrogen (1 possibility)

$C_{1-7}$ hydrocarbyl (261 possibilities)

$C_{1-7}$ hydroxyhydrocarbyl (261 possibilities)

$C_{1-7}$ aminohydrocarbyl (261 possibilities)

$C_{1-7}$ hydrocarbylaminohydrocarbyl (68,121 possibilities)

$C_{1-7}$ dihyrocarbylaminohydrocarbyl (8,889,790 possibilities)

$C_{1-7}$ halohydrocarbyl (1044 possibilities)

$C_{1-7}$ hydrocarbyl substituted with $C_{3-6}$ alicyclichydrocarbyl (1566 possibilities)

These add up to 8,961,304 possibilities.

To simplify, we assume:

1. Only 1 alkenyl and 1 alkynyl is derived from alkyl,
2. $R^1$, $R^2$, and $R^3$ only have 2, 3, 4 substitution on the phenyl,
3. any substituent only substitutes once and at only one position, (i.e. n-butyl only gives *n*-butylchloride, not *n*-butyl-1-chloride, *n*-butyl-2-chloride, dichloro, trichloro, etc.), and
4. $C_{3-6}$ alicyclic only includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, and cyclohexenyl.

All of these assumptions make our estimate much lower than the actual number.

Although Reiter does not say, we assume that for a group like "hydrocarbylaminohydrocarbyl" both hydrocarbyls in the moiety have the number of carbon atoms designated for the associated "hydrocarbyl."

For $R^4$ and $R^5$, symmetry divides the number of possibilities in half (e.g. $R^4$ = H, $R^5$ = Me is the same as $R^4$ = Me, $R^5$ = H).

Thus, the number of possible compounds is the product of the number of possibilities for each variable group divided by 2, i.e.:

$(52,581,035)(52,581,035)(52,581,035)(942)(62)(8,961,304)/2 = 3.8 \times 10^{34}$

**Possibilities for Alkyl:**

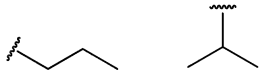
C1-8 alkyl =

C1 alkyl: methyl

C2 alkyl: ethyl

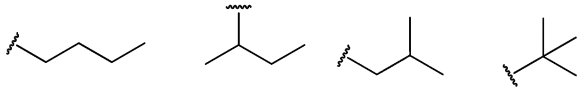
C3 alkyl:

2 possibilities



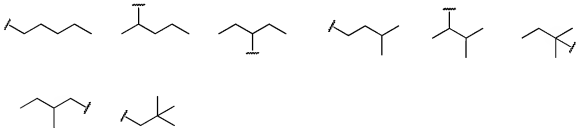
C4 alkyl:

4 possibilities



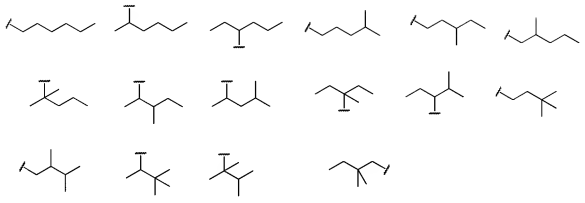
C5 alkyl:

8 possibilities



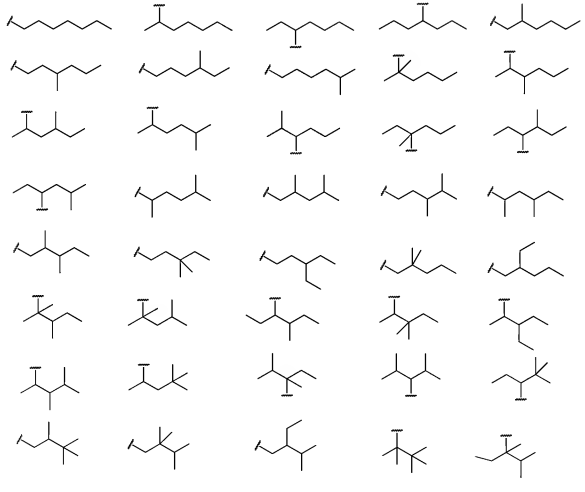
C6 alkyl

16 possibilities



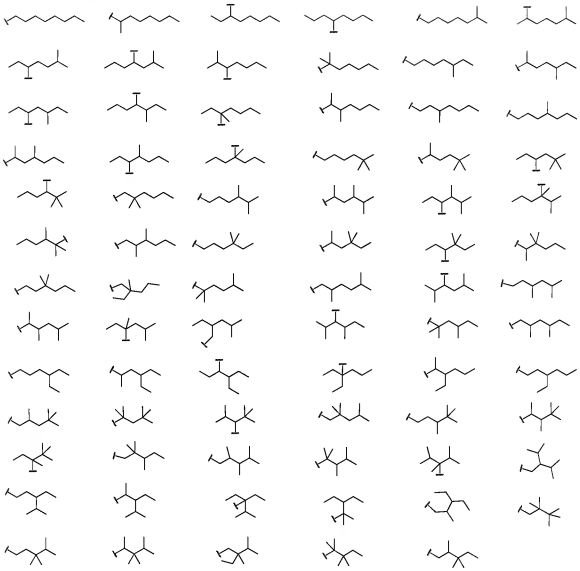
C7 alkyl

48 possibilities



C8 alkyl

77 possibilities



**B. THE CLAIMED COMPOUND HAS UNEXPECTED RESULTS COMPARED TO THE CLOSEST PRIOR ART COMPOUND.**

The presently claimed compound is effective in reversing allodynia, while the closest prior art compound is not. Usually, a showing of unexpected results is sufficient

to overcome a *prima facie* case of obviousness. MPEP 2144.08 (b)(6). Since these results were presented in the patent application, they should have been considered before any rejection was made. 1-(2-Fluorobenzyl)-3-(2-hydroxyethyl)-thiocarbamide is the closest prior art compound to the presently claimed compound. This compound is depicted as "Formula 4" in the present application. (Specification, 18). The specification reports that the compound of Formula 4 had no analgesic activity at doses up to 3 mg/kg (p. 24, lines 27-28), but that the claimed compound ("Formula 2") reversed allodynia by from 90% to 95% at 100-300 µg/kg (p. 25, lines 2-3). Thus, the claimed compound has unexpected results as compared to the closest prior art compound, and the claims are not obvious.

**C. THE REJECTIONS AND RESPONSES MADE IN THIS CASE DO NOT JUSTIFY A LONG PROSECUTION HISTORY.**

Applicants respectfully point out that this reference was submitted to the Office well over six years ago in an IDS. Applicants also summarize the nearly five year-long prosecution history below.

**First Office Action**

- July 2, 2002: Examiner rejects claims 1-3 as anticipated by Chemical Abstracts 93:132428.
- October 24, 2002: Applicants argue that the reference does not anticipate.

**Second Office Action**

- January 29, 2003: Examiner rejects claims 1-3 as being obvious in view of Chemical Abstracts 532428.
- June 30, 2003: Applicants argue against the obviousness rejection.

**Third Office Action**

- July 1, 2004: Examiner rejects claims on same grounds.
- October 4, 2004: Applicants respond with additional arguments, and include a declaration providing unexpected results.

**Fourth Office Action**

- January 28, 2005: Examiner withdraws obviousness rejection, applies a non-statutory double patenting rejection.
- March 17, 2005: Applicants file a terminal disclaimer.

**Fifth Office Action**

- June 16, 2005: Examiner rejects claims under § 112 for indefiniteness.
- July 11, 2005: Applicants amend.

**Sixth Office Action**

- October 7, 2005: Examiner applies a restriction requirement.
- November 14, 2005: Applicants make an election.

**Seventh Office Action**

- February 27, 2006: Claims rejected as anticipated by U.S. Patent 6,787,517.
- April 21, 2006: Applicants point out that the present application claims priority to 6,787,517, and thus it is not prior art.

**Eighth Office Action**

- July 13, 2006: Examiner makes a non-statutory double patenting rejection.
- September 13, 2006: Applicants file terminal disclaimer.

**Ninth Office Action**

- December 1, 2006: Examiner again rejects claims as being anticipated by U.S. Patent 6,787,517.
- February 9, 2007: Applicants again point out that 6,787,517 is a priority document, and not prior art.

**Tenth Office Action**

- April 19, 2007: Examiner rejects claims as obvious in view of GB 1499485.

Applicants file the present appeal.

The rejections made on this patent application do not justify the long delay in allowing the patent to issue.

Therefore, Applicants respectfully request that the Board direct Examiner to allow the claims.

Dated: July 2, 2007

Respectfully submitted,

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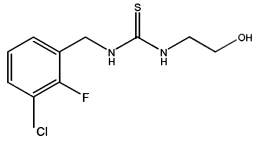
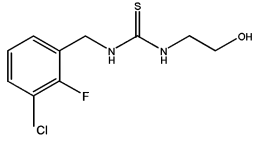
## (8) CLAIMS APPENDIX

1. A compound represented by the formula:




or an alkyl ester, or a pharmaceutically acceptable salt thereof.

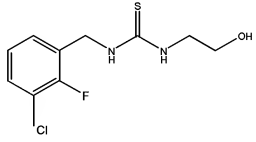
2. A composition comprising one or more chemical entities chosen from a compound according to the formula




an alkyl esters thereof, a pharmaceutically acceptable salt thereof, and a combination thereof; and

a pharmaceutically acceptable excipient for therapeutic delivery of said compound.

3. The compound of claim 1 represented by the formula:




or a pharmaceutically acceptable salts thereof.

## (9) EVIDENCE APPENDIX

No evidence is cited herein.

## (10) RELATED PROCEEDINGS APPENDIX

No related proceedings are cited herein.